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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,667	09/19/2003	Torben Vedel Borchert	5368.220-US	9060

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EXAMINER	
PROUTY, REBECCA E	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/665,667	BORCHERT ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 40-47 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 40-47 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/183,412.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 9/03.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-39 have been canceled. Claims 40-47 are at issue and are present for examination.

The disclosure is objected to because of the following informalities: The first line of the specification should be updated to reflect the current status of the parent applications.

Appropriate correction is required.

The disclosure is objected to because of the following informalities: The key recited on page 6 for the described mutations is confusing. Page 6, line 24 describes the nomenclature that is to be used when defining mutations: "Original amino acid(s): position(s): substituted amino acid(s)". Page 6, line 27-27 recites: "for instance substitution of alanine for asparagine in position 30 is shown as : Ala30Asn or A30N". This example conflicts with the above stated format of reciting mutations. The substitution of alanine for asparagine in position 30 should be written as: Asn30Ala or N30A, **not** Ala30Asn or A30N.

Further the nomenclature key recited on page 7 is inconsistent at lines 6-9, where it is recited "Ala30Asp + Glu34Ser or A30N+E34S representing mutations in positions 30 and 34 substituting alanine and glutamic acid for asparagine and

serine, respectively". As per the above format, "Original amino acid(s): position(s): substituted amino acid(s)", stated on the top of page 3, Ala30Asp + Glu34Ser or A30N+E34S **should** represent mutations at positions 30 and 34, substituting asparagine and serine for alanine and glutamic acid, respectively.

Appropriate correction is required.

Claims 40-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an α-amylase having at least 90% homology to SEQ ID NO:2 and comprising one or more mutations selected from the group consisting of deletion of the residue equivalent to R182 of SEQ ID NO:2, deletion of the residue equivalent to G182 of SEQ ID NO:2, substitution of the residue equivalent to G149 of SEQ ID NO:2, and substitution of the residue equivalent to H107 of SEQ ID NO:2 does not reasonably provide enablement for any α-amylase having at least 80% homology to a parent Termamyl-like α-amylase and comprising of one or more mutations selected from the group consisting of deletion of the residue equivalent to R182 of SEQ ID NO:2, deletion of the residue equivalent to G182 of SEQ ID NO:2, substitution of the residue equivalent to G149 of SEQ ID NO:2, and substitution of the residue equivalent to H107 of SEQ ID NO:2. The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 40-47 are so broad as to encompass any variant of a parent Termamyl-like α-amylase having at least 80% identity to said parent α-amylase and comprising of one or more mutations selected from the group consisting of deletion of the residue equivalent to R182 of SEQ ID NO:2, deletion of the residue equivalent to G182 of SEQ ID NO:2, substitution of the residue equivalent to G149 of SEQ ID NO:2, and substitution of the residue equivalent to H107 of SEQ ID NO:2. It should be noted the term "Termamyl-like α-amylase is defined on page 9 of the specification as an α-amylase which, at the amino acid level, exhibits a substantial homology to Termamyl™, i.e., the *B. licheniformis* α-amylase having the amino acid sequence shown in SEQ ID NO:4, i.e., α-amylases which displays at least 60% identity with at least one of the amino acid sequences shown in SEQ ID NOS: 1-8 and/or displays immunological cross-reactivity with an antibody raised against at least one of said α-amylases, and/or is encoded by a DNA sequence which hybridizes to the DNA sequences encoding these α-amylases. The claimed genera include variants with an enormous number of alterations of the parent

enzyme (which parent enzyme can be selected from an enormously large group of enzymes) as long as amylase activity is maintained. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of variant α-amylases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to only a few representative species of such variant α-amylases each with only a small number of altered amino acids compared to the parent α-amylases.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of

success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass an enormous number of variant enzymes because the specification does **not** establish: (A) regions of the protein structure which may be multiply modified without effecting α-amylase activity; (B) a rational and predictable scheme for major modifications to α-amylases having 60% homology to SEQ ID NO:2 at large numbers of residues with an expectation of obtaining the desired biological function; and (C) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including an enormous number of amino acid modifications of a large number of parent α-amylases

wherein said variant comprising of one or more mutations selected from the group consisting of deletion of the residue equivalent to R182 of SEQ ID NO:2, deletion of the residue equivalent to G182 of SEQ ID NO:2, substitution of the residue equivalent to G149 of SEQ ID NO:2, and substitution of the residue equivalent to H107 of SEQ ID NO:2. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of α-amylases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

While it is acknowledged that the prior art provides substantial guidance with regard to mutation of α-amylases, the instant rejected claims all include many variants with more than minor modifications to the structure of a wide variety of parent enzymes, which themselves may have substantial modifications in structural features from the enzymes which have been modified in the prior art. As such the amount of experimentation required to make and use the currently claimed scope is still deemed to be undue.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent..

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 40-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Bisgard-Frantzen et al. (WO 96/23873).

Bisgard-Frantzen et al. teach variants of a parent Termamyl-like α-amylase wherein the variant has α-amylase activity and at least one altered property such as decreased Ca^{+} dependency, thermostability, or alterations in substrate specificity, substrate binding, substrate cleavage pattern, pH/activity profile and/or pH/stability profile. The parent Termamyl-like α-amylases include and/or are derived from a

strain of *B. licheniformis, B. amyloliquefaciens, B. stearothermophilus, Bacillus* sp. NCIB 12512 or NCIB 12513. Bisgard-Frantzen et al. specifically teach variants comprising deletions of residues 181 and 182 as well as many other mutations (see page 16).

Claims 40-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Suzuki et al.

Suzuki et al. teach a mutant *Bacillus amyloliquefaciens* α-amylase (BAA) with increased thermostability in which amino acid residues 176 and 177 (equivalent to residues 181 and 182 of SEQ ID NO: 2) are deleted.

Claim 46 is rejected under 35 U.S.C. 102(b) as being anticipated by Svendsen et al. (WO 96/23874).

Svendsen et al. teach variants of a parent Termamyl-like α-amylase wherein the variant has α-amylase activity and at least one altered property such as decreased Ca^{+} dependency, thermostability, or alterations in substrate specificity, substrate binding, substrate cleavage pattern, pH/activity profile and/or pH/stability profile. The parent Termamyl-like α-amylases include and/or are derived from a strain of *B. licheniformis, B. amyloliquefaciens, B. stearothermophilus,*

Bacillus sp. NCIB 12512 or NCIB 12513. Svendsen et al. specifically teach variants comprising substitutions of H105 of *B. licheniformis* α-amylase (equivalent to residue 107 of SEQ ID NO: 2), see page 20.

Claims 46-47 are rejected under 35 U.S.C. 102(e) as being anticipated by Svendsen et al. (US Patent 6,022,724).

Svendsen et al. teach variants of a parent Termamyl-like α-amylase wherein the variant has α-amylase activity and at least one altered property such as decreased Ca^{+} dependency, thermostability, or alterations in substrate specificity, substrate binding, substrate cleavage pattern, pH/activity profile and/or pH/stability profile. The parent Termamyl-like α-amylases include and/or are derived from a strain of *B. licheniformis, B. amyloliquefaciens, B. stearothermophilus, Bacillus* sp. NCIB 12512 or NCIB 12513. Svendsen et al. specifically teach variants comprising substitutions of H105 of *B. licheniformis* α-amylase (equivalent to residue 107 of SEQ ID NO: 2) including specifically substitutions with phenylalanine or lysine (see column 20, lines 6-27).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Svendsen et al. (WO 96/23874).

Svendsen et al. (WO 96/23874) is discussed above. They do not specifically disclose the replacement of H105 with I, L, V, F, Y, or K. However, as Svendsen et al. have identified the specific amino acid residue to be modified, it would have been obvious to one of skill in the art to replace that amino acid residue with any of the remaining 19 natural amino acids. Furthermore, on page 31, Svendsen et al. explicitly suggest replacing residues such as H105 with an amino acid which is bulkier than that which naturally occurs. Thus this would clearly lead the ordinary artisan to replace H105 with amino

acids such as phenylalanine or tyrosine which are bulkier than histidine.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (571) 272-0937. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Rebecca Prouty
Primary Examiner
Art Unit 1652